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THE FUNCTION OF THE CORONARY MICROCIRCULATION OF THE LEFT VENTRICLE

RICHARD ALBERT MOGGIO

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THE FUNCTION OF THE CORONARY MICROCIRCULATION OF THE LEFT VENTRICLE

Richard Albert Moggio

A thesis submitted to the Yale University School of Medicine as required for the degree Doctor of Medicine

Yale University School of Medicine

1971

DEDICATION

To R. Vieussens, forgotten
sixteenth century anatomist
and discoverer of the
thebesian vessels.

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INTRODUCTION

The coronary circulation is unusual in that it does not completely follow normal circulatory pathways found in smooth or skeletal muscle, i.e., blood moving from artery to arteriole to capillary to venule to vein. In cardiac muscle this orderly pattern is intercepted by channels which connect the coronary vascular system with the cavities of the heart: sinusoids wandering through the left ventricular myocardium, and thebesian veins draining blood from much of the right ventricular myocardium (19), (21), (28).

The heart's circulatory pattern has been explained from an evolutionary point of view by tracing the development of the myocardial vasculature from the early vertebrate hearts which had no coronary arteries, but were supplied by blood from the ventricular lumen which washed into and out of the myocardium and bathed the muscle bundles with oxygenated blood (32). As animals ascended the evolutionary ladder, however, heart muscle became more and more compact, compressing the sinusoids so that blood could no longer enter and egress freely (15), (18). Accordingly, coronary arteries probably developed as the need for an extramyocardial blood supply arose (17), (1).

Several studies have investigated the question of whether the mammalian coronary-ventricular lumen channels are only vestigial remnants of evolutionary development, or whether they are a functional part of the myocardial circulation, playing an important physiologic role in maintaining the heart's viability. Anatomic studies have attempted to define the structure and caliber of these channels. Physiologic studies have shown the passage of dye and radioactively labelled plasma from the left ventricular lumen into the myocardium, and calculations of oxygen saturation differences between the left atrium and the aorta have been employed to determine the amount of flow between the coronary vessels and the ventricular lumen. Clinical and pathologic reports have indicated the possible protective role of these channels in cases of coronary artery narrowing and occlusion (40), (72).

The coronary-luminal channels remain worthy of investigation because of several remaining problems. The actual passage of red blood cells, rather than just dye or plasma, through these channels has not been verified. The relationship between amounts of flow through the channels and varying coronary-ventricular pressure gradients has not been quantitated. The characteristics of

blood flow through the channels have not been fully investigated; whether an "ebb and flow" motion of blood occurs between the ventricular chamber and the myocardium, as in primitive vertebrate hearts; or whether blood can simultaneously enter and leave the coronary circulation through coronary-luminal channels. Finally, few experiments have been performed on intact functioning hearts.

The experiments described in this study were undertaken to investigate further these remaining problems.

REVIEW OF PREVIOUS INVESTIGATION

I

The belief that the coronary arteries have direct vascular communication with the chambers of the heart was first advanced in 1706 by Raymond Vieussens (67) with the publication of a letter in which he described a series of experiments performed on dead human, beef, and sheep hearts. He ligated the superior and inferior vena cavae as well as the pulmonary veins, then injected a solution of alcohol and safranin into the coronary arteries. He observed drainage of the solution into the cardiac chambers not only through the coronary sinus, but also through small ducts in the walls of the atria and ventricles. Dissecting hearts and examining them with a microscope, Vieussens found the small ducts and openings through which his safranin solution drained. In some instances he found small valves over the openings. Extensive study of these ducts led him to conclude that they were continuous with the coronary arteries.

Two years later Thebesius described numerous openings in the auricles and ventricles for the drainage of venous blood (65). He injected water and colored liquids into the coronary sinus and observed its drainage into the

chambers. He concluded these passages serve to drain venous blood only, contrary to the work of Vieussens who had injected the coronary arteries. Thebesius' belief that the vessels were connected only with veins was supported by several other anatomists of the sixteenth century (22), (39), (66); so the work of Vieussens was largely forgotten, with the result that all such communicating channels became known as thebesian veins.

Through the latter sixteenth and most of the seventeenth century, varous reports confirmed or denied the existence of thebesian veins (see discussions in Wearn (70) and Pratt (53)). Of early significance was the work of Pratt (53) who in 1898 provided the first experimental evidence that the thebesian vessels may play a role in the nourishment of the myocardium. After first demonstrating for himself the existence of these vessels he concluded that they open from the ventricles and auricles into a system of fine branches that communicate with the coronary arteries and veins by means of capillaries, and with the veins--but not the arteries--by passages of somewhat larger size. Then, using a freshly extirpated cat heart, he passed a cannula through the pulmonary artery into the right ventricle and occluded all portals of outflow except the thebesians. Fresh defibrinated blood was

then passed into the cannula and distended the ventricle. Within a minute or so, the heart began to beat spontaneously and was maintained by the thebesian circulation for several hours.

In other, similar experiments, Pratt incised the large coronary veins and demonstrated a small but steady stream of venous blood, darker in color than that perfusing through the cannula, issuing from the veins. Under the same conditions, the left descending coronary artery was incised, but blood failed to escape from this vessel. To demonstrate that the mechanical stimulus of distension was inadequate to maintain contractions, Ringer's solution infused under the same conditions failed to maintain myocardial function.

In 1928, Wearn (71) perfused the coronary arteries of isolated human hearts 48 hours post-mortem and observed the perfusate escaping into the chambers of the heart. By measuring outflow from the coronary sinus and veins, and total outflow into the atria and ventricles, he calculated that 60-90% of coronary flow drained through the thebesian vessels directly into the chambers of the heart. Using India ink dye injection, and preparing microscopic sections for histologic study, Wearn found three types of connections between the thebesians and

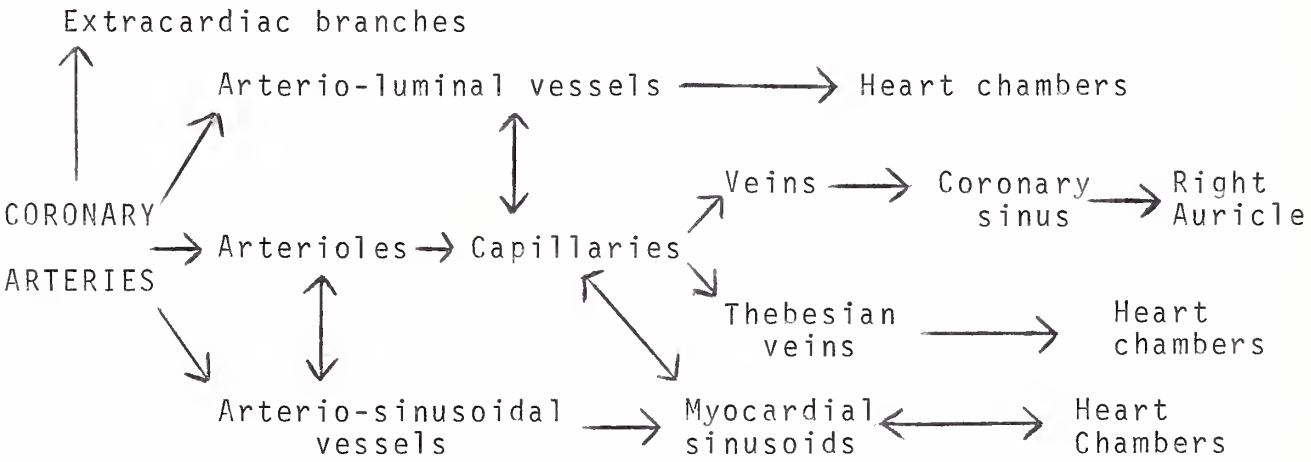
the coronary vasculature: 1) direct connection between arteries and the thebesian vessels; 2) venous connections; and 3) capillaries which run directly into the thebesian vessels. The distribution of thebesians varied greatly but were usually most numerous in the walls of the ventricles, in the apex and around the papillary muscles. Few openings were found in the left atrium. More openings were found on the right than the left side of the heart.

Studies by Wearn and associates in 1933 (72) further elucidated the anatomic nature of the coronary-luminal vessels. Using unselected human hearts obtained at necropsy, they injected both the ventricles and the coronary arteries with thick celloidin fluid mass. Ventricular injection pressure was 160 mm Hg, and coronary injection pressure was 180 mm Hg, which pressures were maintained for 15 minutes before the heart was plunged into ice water, followed by 75 per cent HCl to effect corrosion of the muscle.

The casts made in this manner showed a vast number of inter-communicating channels connecting the coronary arteries with the heart chambers, as described in the work of 1928. Serial microscopic studies of blocks of myocardium revealed several types of communications not

shown previously. The first of these channels were small branches of arteries or arterioles lying near the endocardium which ran a short course and emptied directly into the lumen of the heart. These channels were larger than capillaries but were endothelial-lined, and were called "arterio-luminal" vessels. The second type arose as a branch of an artery or arteriole and soon broke up into sinusoids which lay between muscle bundles and individual muscle fibers. These vessels were termed "arterio-sinusoidal" vessels, and the sinusoids into which they drained were designated "myocardial sinusoids".

On the basis of these studies, Wearn proposed the following scheme:



Blood entering the coronary arteries had possible exits through:

a) arterioles, capillaries, and veins;

1. into the coronary sinus or great cardiac veins and thence into the right atrium, or
2. through the thebesian veins into the heart chambers;

b) the "arterio-luminal" vessels directly into the heart chambers;

c) the "arterio-sinusoidal" vessels through the "myocardial sinusoids" into the chambers; and

d) the extracardiac anastomoses (around the great vessels, lungs, and pericardium.)

The first three systems anastomosed with each other. Although experiments were not conducted to determine the amount or direction of flow through these channels, it was speculated that these communicating luminal vessels were an integral and functioning part of the myocardium, able to contribute to its nourishment.

These early studies of Wearn and Pratt, then, provided a crude anatomic and physiologic basis for the active participation of the coronary-luminal vessels in the overall myocardial circulation. These were not in vivo studies, however, and used revived isolated hearts with artificial circulations. The cast digestion technique of Wearn employed high pressures (160-180 mm Hg) to fill the channels, and though this technique demonstrated the potential patency

of these channels, it gave little indication of their function under normal physiologic conditions.

Eckstein (11), working with Wearn, attempted to determine whether the thebesian vessels of the right ventricle could conduct blood from the ventricular lumen to the myocardium. Dye was injected into the right ventricle of a revived isolated canine heart. RV pressure was varied by a bulb reservoir connected by a cannula to the pulmonary artery. When the India Ink dye was injected into the right ventricle of the beating heart, no capillary injection occurred when the RV systolic pressure was below LV systolic pressure. However, complete capillary injection with dye was produced when both RV systolic and diastolic pressures exceeded those in the LV. From these results it was concluded that in the normally beating heart (RV systolic less than LV systolic pressure) the myocardium received no nourishment from the thebesian veins or luminal vessels.

Katz and associates (34), investigating blood flow through the coronary vessels, found that coronary sinus drainage often exceeded coronary artery inflow and speculated that thebesian vessels may play a part in supplying the myocardium with blood. Bohning, Jochim, and Katz (5) explored the question by maintaining a beating heart-lung

preparation in which a support dog provided blood to the completely isolated coronary circulation. The coronary arteries were cannulated and perfused from the support dog. The superior vena cava was injected with bismuth particles or a suspension of staphylococci. Blood returning to the cannulated coronary sinus was collected and analyzed for the injected substances. They repeatedly found bismuth or staphylococci in this collected blood, when right and left ventricular systolic pressures were less than coronary systolic pressure. Foreign material was identified histologically in myocardial sinusoids, and in the intramural spaces of the coronary arteries, veins, and capillaries.

The experimenters concluded from this study that blood can pass from the heart cavities into the coronary circuit in the living "normal" heart even when the pressure in the coronary arteries is higher than that in the right or left ventricle. There exist several difficulties, however, in the translation of these results to what occurs in the "normal" heart. The experimenters acknowledged difficulty in detecting bismuth histologically, and their published results showed little injection of the capillaries (as pointed out by Eckstein (11)). Secondly, since the coronary circulation was perfused from a second dog,

the time and pressure relations between the coronary flow and ventricular contractions were not normal. Finally, in contrast to Eckstein's experiment, this study did not attempt to separate the circulation of the right and left ventricle.

Various anatomic studies have investigated the anastomoses of the coronaries with each other, extracardiac vessels and the chambers of the heart. None further elucidated the cellular structure of Wearn's "arterio-luminal", "arterio-sinusoidal", and "myocardial sinusoids" designations, and less importance came to be attached to the exact course of these channels and their coronary connections. Rather, more emphasis has been placed on the caliber of the channels and their connection with myocardial capillaries; i.e., on their ability to conduct blood cells and to provide nourishment via capillaries, rather than just passing through the myocardium in shunt-like fashion.

Prinzmetal (54) perfused the coronary circulation with glass spheres of known microscopic size. These perfusions demonstrated luminal channels up to 200μ in diameter. MacLean (42), using a similar technique, was unable to find evidence of arterio-luminal shunts greater than 20μ in diameter. It is known, however, that solid,

nondistortable spheres do not accurately reproduce the flow of red blood cells through small vessels and capillaries, so the true functional caliber of the coronary-luminal channels could not be determined from these experiments.

Butterworth (7) used a self-illuminating cardioscope in dogs and patients to study venous drainage into the left side of the heart. He observed a steady flow of mixed venous blood streaming from numerous endocardial openings about 0.5 mm in diameter. These openings had no regular distribution within the left auricle, were about 1-3 cm apart, and were most numerous on the anterior wall and lower part of the interatrial septum. He saw no venous streams in the left ventricle, but questioned their presence because of the difficulty visualizing the left ventricular wall among the swirls of chamber blood. Butterworth estimated that about 2 cc/min was draining into the left atrium, about 4% of coronary flow.

Injection and corrosion techniques, as described by Kazzaz (35) and Stern (64), have been used to study the coronary-luminal channels. Christensen (9) demonstrated continuity between the venous sinuses of the ventricular myocardium and the lumen of both the right and left ventricle. He also showed that much of the interatrial blood

supply is drained by vessels which empty directly into both the right and left atrial chambers.

In a series of injection studies with vinylite resins, James (29), (30), (31) showed that thebesian veins were more prominent in the right atrium than the left, and noted that the thebesians of the right atrium were often so numerous as to coalesce and to cast as a sponge-like trabeculae of plastic. Hood (25), on the other hand, found that 96% of all blood supplying the left ventricle drained by way of the coronary sinus, and that the coronary sinus blood was composed primarily of left myocardial blood. Consequently, most right ventricular blood drained via the thebesians into the right atrium. Hood's results conflict with those of Moir (48), who injected I^{131} albumin into the septal artery and measured time-concentration dilution curves recorded in the pulmonary artery. He found that 60% of septal artery flow, about 13% of total left common coronary flow, drained directly into the right ventricle via thebesians.

Although the cast corrosion techniques have given the naked eye a view of the coronary-luminal vessels, they have not contributed to an understanding of the functioning of these vessels in the intact working heart. Different injection materials of varying viscosity and

penetrability injected under various pressures have led to inconsistent results with respect to the number, location, and caliber of communicating channels.

The method of dye injection was used again by Roberts to determine the direction of flow through the thebesians (59). With a bottle and bag device in the pulmonary artery to prevent blood (or dye) leaving the right ventricle from mixing with blood in the left atrium and ventricle, dye was injected into the right ventricle. Blood was found in the myocardium only when pressure in the right ventricle exceeded that in the left ventricle (and coronary arteries).

In a second series of experiments on 35 dogs, under conditions of unaltered pressure gradients, dye injected into the anterior descending coronary artery passed into the cavity of the left ventricle (60). Then, to determine whether blood would flow from the left ventricle to the myocardium, Roberts injected dye into the left ventricle immediately after the main coronary arteries, aorta, vena cavae, pulmonary artery and veins were ligated. Dye was found to appear immediately after injection, appearing first in the apex of the left ventricle, and flowing toward the base through the coronary arteries and veins. Pressures of 120 mm Hg were used to inject the dye (56).

From these experiments Roberts concluded that coronary-luminal vessels can conduct blood from the cavity of the left ventricle, into the myocardium under circumstances in which the pressure in the ventricle is greater than that in the coronary arteries (57). He has, however, emphasized their possible role as auxiliary sources of nourishment or drainage for the left ventricle, serving to protect the inner portion of myocardium from infarction following coronary artery thrombosis (63).

Roberts' work was the first extensive investigation of pressure-flow relationships within the thebesians. However, dye, not blood cells, was used to trace flow. Dye may have traversed spaces through which cells would be unable to travel. Observation of dye appearing in vessels or within the myocardium was only a qualitative estimate; the amount of flow was unknown. Further, since only the outer aspect of the myocardium and superficial coronary vessels were observed, it is unknown how much blood may have entered the inner layers of myocardium, and whether any of that dye entered capillaries and drained through deep veins to the right side of the heart, or whether it drained back into the left ventricle unnoticed. Finally, injection pressures and ligation of great vessels produced a non-physiologic cardiac situation,

the results of which cannot be easily carried over to the normally intact working ventricle.

II

Recently, several studies have attempted to quantitate the amount of blood carried by the coronary-luminal vessels of the left atrium and ventricle. Ravin (55) calculated the contribution of the thebesian vessels to "physiologic shunting" in man; i.e., the amount of coronary blood draining into the left atrium or left ventricle. The pO_2 in the aorta was compared with the pO_2 in the left atrium. Using this oxygen difference, he calculated that an average of 0.26% of coronary flow drained back into the left atrium, with a range of 0.12% to 0.43%. This amount reflects drainage into the left atrium only, since drainage into the ventricle would already be reflected in a lowered pO_2 of the aorta, and be eliminated from the calculations. Perhaps a better estimate could have been obtained from pO_2 values in the pulmonary veins, left atrium and left ventricle. Further, an O_2 difference between aorta and atrium depends on blood travelling through capillaries and exchanging oxygen with the myocardial tissue. Although this exchange is the prime consideration from the viewpoint of shunting and myocardial metabolism, it does not account for any blood flowing through coronary-luminal vessels that was

not used metabolically by the myocardium (e.g., Wearn's "arterio-luminal" vessels).

Brandfonbrener (6) calculated the total amount of blood flow to the left ventricle from sources other than the left coronary artery. The left coronary was cannulated and perfused from a support dog while Evans blue was injected into the experimental dog's systemic circulation. After mixing, simultaneous blood samples were drawn from the systemic circulation and coronary sinus. A series of calculations using flow rates and dilution principles enabled the amount of flow to the left ventricle from the experimental dog's systemic circulation to be determined. This amount was found to be over 1 ml/min/100 gms heart tissue in only 1 of 13 experiments. The amount of flow was somewhat higher when aortic pressure exceeded coronary pressure than when coronary exceeded aortic pressure, but was not appreciably increased. This experiment measured extracoronary blood that drained via the coronary sinus only, and did not include thebesian drainage to the right side of the heart, which may have been significant and have indicated a much higher contribution of blood from sources other than the left coronary artery. Further, use of a support animal distorted the normal pressure-flow relationships between the coronary artery and ventricular

contractions.

In Japan, Watanabe (70) used the dye-injection method and time-concentration dilution curves to quantitate thebesian flow in the fibrillating heart and the isolated beating heart. In one experiment, a portion of dye injected into the left coronary artery was found to enter the aorta after a time delay shorter than the time delay for dye injected into the right auricle to enter the aorta, indicating that some coronary blood (dye) had "short-circuited" through the left ventricle and atrium into the left heart chambers and then to the aorta.

In the fibrillating heart, dye was injected into the left coronary artery, and after several minutes, both ventricles were punctured, blood drained from them, and dye concentration determined from aliquots of the ventricular blood. The proportion of dye appearing in left ventricular blood determined the amount of flow through coronary-left ventricular luminal vessels. This flow ranged from 0.5% to 11%, and averaged 3.5% in 7 experiments. Pressures in the coronaries and ventricles were unknown in this experiment, and no blood was actively flowing through either the coronary vessels or the heart chambers. Hence it is difficult to draw any conclusions about normal coronary-luminal flow from this experiment.

Using an isolated, perfused, beating heart, Watanabe injected dye into the left coronary artery and collected outflows from the pulmonary artery and aorta. Dye concentration determinations in these collections revealed a shunt flow from coronary to left ventricular lumen ranging from 1% to 15%, and averaging 3.8% in 15 experiments. This value was approximately that determined in the fibrillating heart.

Moir (45) refined the dye dilution technique of Watanabe. I^{131} labelled albumin was used instead of dye. The intact working canine heart was studied by cannulating the left coronary artery and perfusing it from a pressure reservoir while I^{131} albumin circulated systemically. Any radioactivity appearing in the myocardium would have passed directly into the myocardium from the lumen.

At normal coronary and left ventricular pressures, 0.40 ml/100 gm heart tissue, or 7% of coronary flow, was contributed by labelled luminal blood. This amount was not increased by lowering coronary pressure below ventricular systolic pressure, but did increase to 0.92 ml/100 gm heart tissue after total occlusion of the coronary artery. This amount was insufficient to prevent myocardial deterioration after acute occlusion. Moir concluded that a small amount of blood passes directly from the lumen to

the myocardium, with normal pressure-flow relationships of coronary and left ventricle activity, and that although this amount would not prevent deterioration in dogs with normal coronary arteries, its magnitude and effect in chronic coronary occlusive disease might be significant in protecting the myocardium.

Again using I^{131} labelled albumin, Moir and associates (47) attempted to determine patterns of thebesian drainage in each of the left coronary arteries. The labelled albumin was injected into one branch of the left coronary artery. Time-concentration curves were recorded in the aorta, pulmonary vein, left atrium, or aortic root after injection. In each case large broad peaks were found, representing the major drainage of blood through the coronary sinus to the right heart, through the lungs and back to the left ventricle and aorta. Small, earlier peaks of radioactivity represented "short-circuited" blood draining directly from the coronary vessel into the left heart. Curves taken in the left atrium, though difficult to interpret because of variable mixing in the chamber, enabled left atrial drainage to be separated from left ventricular drainage.

This study showed that in the normally beating heart, thebesian drainage from the left coronary artery to left

heart was about 2%. Most of this drainage was from the left circumflex branch and the left anterior atrial artery. Only small and occasional drainage from the septal artery was found, and no drainage into the left heart from the left anterior descending branch was demonstrated. Since early peaks were recorded in the left atrium in almost all instances, it was concluded that most drainage to the left heart was into the atrium, though left ventricular drainage could not be excluded.

A third experiment by Moir and DeBra (46) demonstrated the possibility of reverse flow in the coronary-luminal vessels. $Rb_{86}Cl$ was mixed with saline and infused at a constant rate for a period of one minute into the superior vena cava of a dog. The right coronary artery had been ligated and the left coronary was perfused from a separate constant pressure reservoir which contained no radioactive material. The hearts were then extirpated and cylindrical biopsies taken from areas of the heart. A scintillation counter determined the radioactive content of the myocardium. These results showed that $Rb_{86}Cl$ is taken up by the myocardium, and to a greater extent in the left ventricle than the right ventricle.

In this experiment as well as those using I^{131} labelled albumin, the labelled element was not attached to

the blood cell and could have crossed the endocardium by diffusion, as the authors point out. Flow determined by this technique may not reflect actual flow of red blood cells through the endocardium.

Myers and Honig (49) employed a technique essentially similar to Moir's to study lumen to myocardial flow. The left coronary arteries of dogs were perfused with unlabelled blood while $Rb_{86}Cl$ was administered systemically. Perfusion rate was adjusted so that mean coronary and aortic pressures were equal. After 2 min of perfusion, sections of myocardium were removed from the extirpated heart. The amount of radioactivity in the myocardium was determined at different distances from the lumen of the ventricle. The luminal blood flow throughout the entire myocardium amounted to 4% of coronary flow. The concentration of Rb_{86} fell rapidly with distance from the lumen, but some isotope could be detected three-fourths the way across the wall. Rb_{86} penetrated deeply beneath the papillary muscles, and provided a significant amount of blood flow to these structures.

In an effort to demonstrate continuity between the luminal vessels and the general capillary bed, attempts were made to detect $Rb_{86}Cl$ in the coronary veins. None was found, and it was suggested that the blood moves in

an "ebb and flow" manner in and out of the myocardium and luminal vessels.

As in Moir's experiment, the labelled element was not attached to the cell. Myers and Honig calculated, but did not experimentally demonstrate, that Rb_{86} would be unable to diffuse more than 65 microns into the myocardium. Since Rb_{86} was found more than 1 cm from the lumen, it was postulated that channels (i.e., luminal vessels) must exist for its inward transport.

The distribution and drainage patterns of coronary flow were studied in the living isolated canine heart by Hammond and Austen (24). Before commencing perfusion through the aortic root, the mitral and tricuspid valves were occluded and catheters placed in the separated heart chambers and the coronary sinus. Total and individual coronary distribution were then measured by timed volume collections from each catheter. PO_2 measurements determined whether blood had passed through a capillary bed. The results are shown below:

Blood pO_2 Values

Aortic root	161	Right Ventricle	60
Coronary sinus	62	Left Ventricle	84
Right Atrium	65		

PERCENT DRAINAGE

	Coronary Sinus	Rt. Atrium Via Anterior Cardiac Veins	Rt. Ventricle Via Thebesian Veins	Lt. Ventricle Via Myocardial Sinusoids
Total Coronary Artery Flow	49	24	22	5
Left Coronary Artery Flow	52	17	25	6
Anterior Descending Artery Flow	48	12	34	6
Circumflex Artery Flow	58	23	12	7
Right Coronary Artery Flow	7	75	15	3
Septal Branch Artery Flow	9	7	63	21

These results indicated that three-fourths of coronary flow enters the right atrium through the standard capillary-venous system and the remainder drains into the ventricular lumens. No drainage was found into the left atrium. It was concluded that the sinusoidal system of the left ventricle, because it partially desaturates the blood, is different from the thebesian system of the right atrium and ventricle, and is capable, in some degree, of contributing to myocardial nutrition. The finding of partially desaturated blood in the left ventricle did not fully exclude the possibility that some of the coronary-luminal

vessels drained through capillaries while others simply shunted blood from arteriole to lumen, vis a vis the "arterio-luminal" shunts of Wearn. It did, however, demonstrate the difference in circulatory pathways between the right and left side of the heart, a difference most likely related to the phylogenetic development of the heart and coronary vessels.

III

While much research was being carried out to determine the physiologic function of coronary-luminal channels, several experimental attempts were made to utilize and expand these channels as a source of augmented myocardial nourishment.

Vineberg (68) treated acute experimentally produced myocardial infarction by endocardial and epicardial resection. Ligation of the anterior descending artery produced a visible 5 x 3 cm area of infarction. A bore instrument passed through this area was used to remove a 3/8" diameter section of endocardium. After the tract bleeding was controlled, the epicardium was removed from the entire left ventricle. The color of the infarct immediately changed from blue to red as blood seeped through the sinusoidal spaces within the myocardium. Nine of 21 dogs survived the procedure for a period of 30-60 days be-

fore sacrifice. In several hearts the cored-out tracts was still patent, and microscopic sections showed thin-walled trabeculated spaces filled with red blood cells and surrounded by healthy myocardium.

Animals sacrificed at a later date showed a closed off tract replaced by blood vessels, fibrous tissue and fat with healthy myocardial fibers on either side of the obliterated tract. It was not known in this experiment the extent to which epicardiectomy promoted the formation of collateral circulation to the heart, or how much blood around the tract came from the lumen of the ventricle compared with inter-coronary anastomoses and sinusoidal inter-communications. Nonetheless, the procedure was of value in increasing survival from acute infarction. Roberts (49) performed a similar procedure by multiple endocardial punctures, which increased the amount of blood flow to the myocardium.

Similarly, Sen (62) created multiple transmyocardial acupunctures in dogs after ligating major branches of the left coronary artery. Each puncture site (about 20 per square centimeter) produced a spurt of blood during systole for a few minutes and then stopped bleeding. Animals were sacrificed or died at intervals of from 2 to 8 weeks. The two week mortality after ligation of the anterior de-

scending artery was reduced from 75% to 25% by puncture, and 55% of animals with acupuncture survived for 8 weeks, compared with 5% survival without puncture. The mean area of infarction was reduced by two-thirds, and no infarcts were found in 60% of the acupunctured hearts.

Dye injection and serial sections showed that in the area of acupuncture, most of the tissue was supplied directly from the ventricular cavity through numerous interconnecting sinusoids interlacing with the puncture tracts. The tracts remained open for at least 8 weeks and contained numerous red blood cells. Since this experiment was conducted on snake hearts, the immediate applicability to man was uncertain. The number of sinusoidal channels in the snake myocardium compared with the dog's or man's was unknown. Further, the effect of the procedure of the stimulation of collateral circulation to the infarcted area was not determined.

Using the same procedure in dogs, Sen (61) found a survival rate of 60% compared with 5% in dogs following ligation of the left anterior descending artery. Again, patent acupuncture tracts were found 18 weeks after the procedure. Some tracts had generated an endothelial lining and had formed communications with sinusoids within the myocardium.

Transmyocardial acupuncture following acute ischemic challenge performed experimentally by Wakabayashi (69) and Khazei (36) have shown similar results. These workers found that the puncture tracts often became filled with fibrin clots after several days, then became recanalized and formed links with the intra-myocardial sinusoids and myocardial vasculature to provide collateral circulation to the ischemic area.

Goldman and associates (16) in 1956 inserted U-shaped carotid artery grafts and polyethylene tubes into the myocardium. About ten openings were made into the loop portion of the graft, which was threaded into the area of myocardium supplied by the left anterior descending artery. The loop of the U lay free in the ventricular cavity and the ends were sutured loosely to the epicardium. Three weeks later the anterior descending artery was ligated. A similar procedure was performed with 3 cm sections of perforated polyethylene tubing.

Examination of the heart five days after ligation showed that the animals with implanted U-shaped arterial grafts showed a survival rate of 85% compared with 39% in a control group. The size of infarcted area was smaller in the implanted animals. In most animals, the arterial graft was still patent and had formed collateral

communications with the coronary vasculature. Contributing to the myocardial blood supply, hence to the survival in the implanted animals, was the formation of extensive vascular adhesions from the pericardium to the site of implantation. Dogs with implanted polyethylene tubes showed no better survival than controls, and all these tubes became thrombosed, shortly after implantation.

In a similar experiment by Massimo and Boffi (43), a T-shaped plastic tube was inserted into the myocardium. The vertical branch was connected directly with the left ventricular cavity, while the horizontal branch was embedded in the myocardium. No ischemic challenge was imposed, and post mortem examination from 2 days to 6 months after surgery showed the tube to be endothelial-lined and unobstructed in 80% of cases.

Although both of these implant experiments, as well as the acupuncture studies, produced increased blood flow to the myocardium, it is difficult to separate the benefits of blood derived directly from the graft from blood arriving via newly stimulated inter-coronary anastomoses and extra-coronary pericardial vascular adhesions. This problem is illustrated by the fact that survival was increased despite occlusion of the grafts and thrombosis of the puncture tracts. The ultimate fate of all the grafts and punctures

is endocardial scarring and closure (2).

In contrast to the work of Goldman, Massimo, Sen and others, Pifarre (52) has rejected the notion that blood can enter the myocardium from the left ventricular cavity at any phase of the cardiac cycle. Repeating the transmyocardial acupuncture studies, he injected the hearts after sacrifice 40 to 180 days after puncture and found coronary collateral anastomoses in every chronic survivor. In no case did Schlesinger mass demonstrate the patency of puncture tract. Neither the mortality nor the size of infarct was reduced in Pifarre's study.

In a second study, Pifarre (51) anastomosed the cephalad end of a jugular vein segment to the descending aorta, and implanted the free end into the posterior myocardium. After 1-6 months radiographs showed collateral anastomoses between the graft and left coronary artery, so that pressures recorded in the graft reflected pressures applied to intramural vessels during systole and diastole. At the peak of systole intramural pressure was 60-100 mm Hg greater than that in the aorta. During diastole pressure was 20-75 mm Hg less than in the aorta. He concluded that intramural blood flow can occur only during diastole in the left ventricle, and speculated that the increase in blood flow found in the previous experiments was due

primarily to the stimulation of collaterals by operative incisions and ischemia.

That stimulation of collateral vessels increased survival in acupuncture and other experiments designed to increase lumen to myocardium flow cannot be denied. Pifarre's studies, however, measured myocardial pressure in only one portion of the myocardium, and was not designed to measure flow or pressure within the myocardial sinusoids and within the innermost layers of the myocardium. Gregg and Eckstein (20) state that some blood flow from aorta to myocardium may occur during systole. A transmyocardial pressure gradient has been demonstrated by Kirk and Honig (37), (38). Measuring pressure from epicardium to within 7 mm of the endocardium, they found that pressure in the deepest layers exceeded ventricular systolic pressure during one-third of the cardiac cycle. They could not exclude blood flow through the coronary-luminal channels since many of these channels may make connections with the sponge-like mass of inter-communicating subendocardial vessels described by Estes (12) and Farrer-Brown (13), (14), which were beyond the depth measured in their experiment.

EXPERIMENT I

PURPOSE

The purpose of this experiment was to investigate in the intact, working left ventricle the passage of blood through myocardial sinusoids at normal coronary and ventricular pressures, and at coronary pressures above and below ventricular systolic pressures.

MATERIALS AND METHODS

Adult mongrel dogs weighing 20 to 50 kg were anesthetized with 25 mg/kg of sodium pentobarbital. The chests were opened through a median sternotomy and the origins of the right and left coronary arteries dissected and encircled with ligatures. Tourniquet tapes were passed around the superior and inferior vena cava and pulmonary artery. The azygos vein was ligated and the periaortic fat pad removed. The animal was heparinized, cannulas were inserted in both cavae and the femoral artery, and cardiopulmonary bypass instituted with an Olson roller pump and a Temptrol, bubble oxygenator. Left ventricular pressure was monitored by a cannula inserted through the aorta and into the left ventricular lumen.

A cannula, which was connected to the arterial perfusion line, was inserted into the right ventricular outflow tract, advanced into the pulmonary artery and occlus-

ively ligated in place. The right ventricle was vented so that coronary drainage could be collected and measured. Finally, a perfusion cannula which was connected to the arterial pump line and, through a Y connector, to a calibrated, variable pressure reservoir was inserted through a pursestring suture in the aorta, advanced into the orifice of the left coronary artery and ligated in place. The right coronary artery was then ligated.

By switching clamps on the femoral and pulmonary lines, the animal could be maintained either on total cardiopulmonary bypass with the left ventricle performing little work, or on right heart bypass with the left ventricle maintaining systemic circulation. By switching clamps on the feeder lines to the coronary perfusion cannula, the coronary circulation could be maintained either from the pump oxygenator or from the calibrated, variable pressure reservoir. During data collection runs, the left ventricle maintained systemic circulation and pressure, and the left coronary artery was perfused from the calibrated reservoir (Fig. 1).

Balance studies were then performed from a known left coronary artery input while collections from the right ventricular cannula determined the volume of drainage from the coronary sinus, anterior cardiac veins and

thebesian veins. Left coronary artery pressure was varied from 140 mm Hg above to 80 mm Hg below left ventricular systolic pressure (equivalent to systemic systolic pressure during data collection runs) by varying pressure in the blood reservoir.

The method for calculating the % transfer of coronary to luminal or luminal to coronary blood was as follows:

1) Drainage occurring into the left ventricular lumen (coronary inflow greater than right ventricular drainage).

$$100 \times \frac{\text{(coronary inflow-RV drainage)}}{\text{coronary inflow}}$$

2) Contribution of left ventricular luminal blood to coronary circulation (right ventricular drainage greater than coronary inflow).

$$100 \times \frac{\text{(RV drainage-coronary inflow)}}{\text{RV drainage}}$$

Since blood could enter or leave the coronary circulation through sinusoids communicating with the left ventricular lumen, or through extracardiac collaterals such as the aortic root fat pad (which had been removed) or through bronchial artery-pulmonary vein collaterals around the posterior surface of the heart, two groups of animals were studied. The first preparation was that just described and determined the transfer of blood across the

left ventricular myocardium. The second, or control, preparation was identical to the first except that the pulmonary artery was ligated without inserting a cannula, and the left ventricle was vented so as to maintain a pressure of zero in this chamber. Left coronary pressure was then varied from 100 mm Hg above to 85 mm Hg below systemic pressure which was maintained by the bypass pump. Therefore, any extracoronary blood entering the coronary circulation would have to come from collaterals around the pulmonary veins.

At the conclusion of the experiment, each heart was weighed and carefully examined to confirm accurate placement of cannulas and occlusiveness of ligatures.

RESULTS

The data from eleven experimental dogs are included in the results. The average left ventricular output during data collection runs was 1,816 cc per minute with a range of 1300-2800 cc per minute. The average ventricular systolic pressure was 86 mm Hg, with a range for all experiments of 31 mm Hg. Coronary perfusion pressure seemed to affect LV systolic pressure only at very low perfusion pressures (25-35 mm Hg), in which cases LV systolic pressure fell 10-15 mm Hg.

In the experimental dogs, the % drainage of coronary

flow into the left ventricular lumen increased as the coronary to lumen pressure gradient increased (Fig. 2). The slope for each experimental dog was computed by the method of least squares regression. Each slope, intercept and 95% confidence limits, as well as the mean values for all experiments, are tabulated in Table I. Ventricular drainage occurred in all experiments but one. The maximum drainage was 43% in one animal when the coronary pressure was 35 mm Hg over left ventricular systolic pressure. The mean drainage for all experiments was 5% when coronary pressure was 110 mm Hg above LV systolic pressure.

As coronary pressure fell below left ventricular systolic pressure, blood from the ventricular chamber entered the myocardial vasculature and contributed to the total coronary drainage (Fig. 2). The % contribution of left ventricular luminal blood to the coronary circulation reached a high of 38% in one animal when coronary pressure was 35 mm Hg below left ventricular systolic pressure. All animals but two showed a contribution of luminal blood to the coronary circulation. The mean contribution for all experiments was 7.5% when the coronary pressure was 50 mm Hg below left ventricular systolic pressure.

Luminal to coronary or coronary to luminal transfer

of blood did not appear to be related to left ventricular end diastolic pressure. The average LVEDP from 87 determinations was 7.6 mm Hg, with a standard deviation of 6.8 mm Hg.

Data from six dogs are included in the results obtained for control determinations. Sinusoidal flow varied with the coronary-systemic pressure gradient in a similar manner to the experimental group's variation, but the amount of flow was much less. Control data, computed by the same methods used for the experimental group, are presented in Table II and Figure 3. The slopes are considerably less than those of all but one of the experimental animals. Maximum contribution to coronary flow amounted to 2-3% in two of the six dogs.

The mean slopes for the experimental and control dogs are shown in Figure 4. The t-test showed the difference between these slopes to be significant at the $p < .001$ level.

Coronary flow in cc/min/100 gm heart muscle increased as coronary pressure increased. Since ventricular systolic pressures were relatively constant during an experiment, experimental changes in coronary pressure primarily determined the coronary-ventricular systolic pressure gradient; hence, coronary flow was also related to the pressure

gradient. Sinusoidal flow in cc/min/100 gm of heart muscle varied with the coronary-ventricular systolic pressure gradient in the same manner as the per cent volume of sinusoidal flow varied with the gradient. Sinusoidal flow was considerably less than coronary flow in most instances (Fig. 5). Calculated slope of the coronary flow line was +1.42, with an intercept of +82 and 95% confidence limits of $\pm$0.003, while the sinusoidal flow line slope was +0.014, with an intercept of -1.0 and 95% confidence limits of $\pm$0.017.

DISCUSSION

The possibility that blood may have entered or left the coronary circulation through extracardiac collaterals rather than the myocardial vascular bed was considered in this experiment. Much is known about the nature and extent of intercoronary anastomoses in humans, (8), (10), (33), (41) but, according to Bery, et. al.,(4) and Horine and Warner (26), it is difficult to draw conclusions about the extent of extracoronary collaterals in the dog. In the human, collaterals from the bronchial and internal mammary arteries have been demonstrated (3), (44), (50). In the dog, anastomoses around the aorta, pericardial reflections, and base of the pulmonary artery, as described by Hudson (27) and Halpern (23), were ligated in this ex-

periment. Judging from the control experiments, the amount of blood contributed to or drained from the coronary circulation by extracardiac collaterals is quite minimal. To be accurate, however, it should be assumed that a small portion of the blood observed to come from the left ventricular lumen when coronary pressure was less than ventricular systolic (hence systemic systolic in collaterals) may have been supplied from extracoronary collaterals.

Several different types of channels have been reported to communicate with the coronary arteries and the left ventricular lumen. These include arterioluminal shunts, thebesian veins, and sinusoids. Based on the previous work of Hammond and Austen (24), which showed that blood entering the left ventricular chamber is neither arterial or venous in nature, it has been assumed that the predominant channels connecting the coronary arteries with the left ventricular lumen are sinusoids. Therefore, for the basis of the remaining discussion, sinusoids will be referred to as the communicating channel through which blood has either entered or left the coronary circulation.

It is, of course, physiologically impossible for pressure at the coronary ostia to be elevated above left ventricular systolic pressure. The purpose of elevating

coronary pressure in this experiment was to demonstrate that flow across the sinusoidal bed increases as the pressure gradient increases.

Situations in which coronary pressure may be lower than left ventricular systolic or systemic pressure are entirely compatible with diseased states, as in coronary artery disease or aortic stenosis. The present experiment indicates that red blood cells are capable of entering the coronary circulation from the left ventricular lumen when coronary pressure is less than ventricular pressure. Further, the transfer of blood into the myocardium began to occur as coronary pressure approached ventricular pressure. This indicates that when coronary and left ventricular systolic pressures are approximately equal (i.e., as occurs normally), a small but continuous amount of left ventricular luminal blood is contributed to the coronary circulation. It seems reasonable to assume that the myocardium closest to the endocardial surface of the heart would receive the most benefit from this source of blood.

Do the sinusoids have a significant protecting effect on the myocardium during periods of decreased coronary flow? It has been shown that the normal working myocardium requires 8-10 ml O_2/min/100 gms of heart muscle

to sustain function (21). This rate is maintained by a coronary flow of 65-100 cc/min/100 gms of heart muscle. During that part of the experiment in which coronary pressure was maintained at 35 mm/Hg below LV systolic pressure, mean flow through the coronary vessels was 35 cc/min/100 gms of heart muscle while mean flow into the coronary circulation from the left ventricular lumen was 7 cc/min/100 gms of heart muscle. Blood flow from both sources theoretically was sufficient to sustain function in only two experimental runs. Since the contribution from both sources falls short of the heart's basic requirement for blood, it would appear that the sinusoids are unable to compensate for the decrease in coronary flow in the acute situation. Despite this, however, the left ventricle continued to maintain a cardiac output of approximately 2000 cc/min without showing signs of failure. The possibility then arises that blood from the left ventricular lumen may be entering and leaving the myocardium in a to and fro motion in much the same way that blood entered and left the primitive vertebrate myocardium. This mechanism would supply much more blood to the heart than could be detected by the present experiment which measured only the net transfer of blood into the coronary circulation. This possibility is suggested by the obser-

vation that transfer of blood into the myocardium from the left ventricular lumen started to occur while coronary pressure was still elevated above left ventricular systolic pressure.

The sinusoids are capable of transporting blood to the myocardium in conditions of reduced coronary pressure and when coronary pressure and ventricular systolic pressure are equal. Whether they transport blood to the myocardium and simultaneously provide drainage at normal as well as altered pressures could not be determined from this experiment. This possibility was to be further investigated in Experiment II. Use of radioactively tagged red blood cells in the systemic circulation would permit two-way transfer of blood to be observed, and would unequivocally demonstrate passage of cellular elements through the sinusoids.

EXPERIMENT II

PURPOSE

The purpose of this experiment was to verify and quantitate by radioactively tagged cells the passage of erythrocytes through the myocardial sinusoids, and to determine, at varying coronary-ventricular lumen pressure gradients, whether two-way transfer of red blood cells in and out of the myocardium can occur.

MATERIALS AND METHODS

The basic preparation was similar to that of Experiment I. Mongrel dogs weighing 20-30 kg were anesthetized with 25 mg/kg of sodium pentobarbital and maintained on positive pressure ventilation to which 6 l/min of oxygen was added. The heart was exposed through a median sternotomy. Extracardiac sources of coronary flow were removed by ligation of the internal mammary arteries at their origins, bronchial and intercostal vessels; and by removal of the fat pad surrounding the aorta and pulmonary artery. The azygos vein was ligated and tourniquet tapes were passed around the superior and inferior vena cavae and the main pulmonary artery. The right and left coronary arteries were then dissected at their origins and encircled with ligatures. The animal was heparinized, cannulae

were inserted in both cavae and the femoral artery, and total cardiopulmonary bypass was begun.

A cannula connected to the arterial perfusion line was inserted through a pursestring suture into the right ventricular outflow tract and advanced into the main pulmonary artery where it was ligated in place. A second arterial perfusion cannula connected to the arterial pump line and, through a Y-connector, to a calibrated variable pressure reservoir, was inserted through a pursestring suture in the aorta, advanced into the left coronary artery and ligated in place. Coronary drainage into the right heart was collected and measured from a cannula inserted through a pursestring suture in the right ventricle (Fig. 6). Systemic, left ventricular and coronary pressures were monitored by cannulas in the femoral artery, left ventricular lumen via the aorta, and coronary artery lines.

Before the experimental runs were begun, the right coronary artery was ligated. A 30 cc suspension of washed erythrocytes labelled with 200 microcuries of Cr^{51} was injected into the oxygenator. Fresh, non-radioactive blood was supplied to the variable pressure reservoir from a support dog cannulated through its femoral artery. The support dog was maintained by replacement transfusions with fresh blood from donor dogs. By switching clamps

on the femoral and pulmonary lines the animal was maintained on total heart bypass or on right heart bypass only with the left ventricle maintaining the systemic circulation. By switching clamps on the coronary arterial lines, the coronary circulation was maintained either from the systemic circulation or from the calibrated, variable pressure reservoir containing non-radioactive blood.

During data collection runs, the left ventricle maintained systemic circulation and pressure and the left coronary artery was perfused with non-labelled blood from the reservoir. Simultaneously, drainage was collected from the right ventricular cannula to determine the volume of coronary drainage to the right side of the heart, and to detect radioactively labelled cells that had entered the coronary circulation from the left ventricular lumen. Left coronary pressure was varied from 90 mm Hg above to 80 mm Hg below left ventricular systolic pressure.

During each experimental run, a 1 cc sample of systemic blood was taken to determine its concentration (cpm/cc) of radioactive blood cells. After the run a similar sample was drawn from an aliquot of right heart coronary drainage.

The amount of blood transported between left ven-

tricular lumen and coronary system was calculated by two techniques: 1) input and output volume studies determined the net amount and direction of luminal flow; 2) the amount of radioactivity in the coronary drainage determined the total contribution of luminal blood (labelled) to the coronary system (unlabelled). In this manner, the possibility of lumen to coronary flow could be detected under conditions in which net flow by volume would be from coronary to left ventricular lumen.

The method for calculating the net per cent transfer of coronary to luminal or luminal to coornary blood by volume technique (% Δ V vol) was as follows:

a) Net drainage into the LV lumen (i.e., coronary inflow exceeding RV drainage).

$$\%\,\Delta V_{vol} = 100 \times \frac{(\text{coronary inflow} - \text{RV drainage})}{\text{coronary inflow}}$$

b) Net contribution of LV luminal blood to coronary circulation (RV drainage exceeding coronary inflow).

$$\%\,\Delta V_{vol} = 100 \times \frac{(\text{RV drainage} - \text{coronary inflow})}{\text{RV drainage}}$$

The total volume of radioactive blood transferred from the left ventricular lumen to the coronary system was determined as follows:

$$\text{Labelled Volume} = \frac{\text{cpm/cc coronary drainage}}{\text{cpm/cc systemic blood}} \times \text{coronary drainage}$$

The per cent transfer of labelled systemic blood from the LV lumen to the coronary circulation (% Δ V rad) was calculated as follows:

$$\%\Delta V_{rad} = 100 \times \frac{\text{Labelled drainage volume}}{\text{coronary input}}$$

Since the animal's coronary circulation was maintained on labelled systemic blood while data collection runs were not being performed, it was necessary to remove this systemic contamination before the actual run began. The run as previously described was thus begun immediately after the coronary input line, coronary arteries, and right heart were flushed free of tagged cells by 200 cc of unlabelled reservoir blood. This decontamination procedure was done under high coronary pressure (150 mm Hg) and total heart bypass and was facilitated by simultaneously flushing 100 cc of saline through the right heart chambers from an elevated reservoir connected by a perfusion line into the right atrium.

To quantitate any residual labelled blood in the coronary system after the decontamination procedure, separate contamination studies were performed on each dog. These studies were identical to the above runs, including the decontamination procedure, except that the left ventricle was bypassed throughout the entire procedure so that no blood flowed from the lumen to the myocardium.

Any labelled blood that remained in the coronary circulation was collected and quantitated in the same manner as for the data collection runs. The calculated volume of residual, labelled blood was then subtracted from the volume determined during the data collection runs, yielding the total amount of blood contributed to the coronary flow by the left ventricular lumen.

RESULTS

Ten successful experiments were conducted. Left ventricular output during data collection runs averaged 1520 cc/min with a range of 1100-2200 cc/min. Left ventricular systolic pressure averaged 78 mm Hg, with a range for all experiments of 42 mm Hg. Coronary perfusion pressure averaged 75 mm Hg, with a range for all experiments of 150 mm Hg, and a range for individual experiments of 100 mm Hg. At low coronary perfusion pressures (30-40 mm Hg), LV systolic pressure fell 10-15 mm Hg; otherwise, the coronary perfusion pressure did not affect LV systolic pressure.

For each run the net per cent volume difference between coronary input and output (%$\triangle$V vol) and total per cent of coronary flow contributed by the left ventricular lumen, according to the concentration of labelled cells in the coronary output (%$\triangle$V rad), were determined. The

results of individual experiments for both techniques are shown in Figures 7 and 8. The slopes for each dog were computed by least squares regression. Calculated slopes, intercepts, 95% slope confidence intervals and mean values for all experiments are tabulated in Tables III and IV. Figure 7 and Table III show data calculated by volume studies, while Figure 8 and Table IV show data calculated by tagged erythrocyte scintillation counting studies.

At coronary pressures above systolic pressure, the net flow through the sinusoids (Fig. 7) was from the coronaries to the left ventricular lumen. The maximum drainage was 7.8% in one animal when coronary pressure was 90 mm Hg above LV systolic pressure. Mean drainage for all experiments was 5.7% at a coronary pressure of 80 mm Hg above LV systolic pressure.

In contrast, flow determined by labelled cell counting (Fig. 8) showed that left ventricular luminal blood entered the coronary system at nearly all coronary pressures above systolic pressure. The amount of flow was about 1.6% of total coronary flow in one animal at a coronary pressure of 80 mm Hg above LV systolic pressure. Mean contribution to the coronary circulation was 0.8% when coronary pressure was 40 mm Hg above LV systolic pressure.

At coronary pressures below systolic pressures, the net flow through the sinusoids (Fig. 7) was from left ventricular lumen to the coronary system. This flow reached 8.2% in one animal when the LV pressure was 80 mm Hg above coronary pressure. Net left ventricular luminal blood contribution to the coronary flow averaged 3% when LV systolic pressure was 60 mm Hg above coronary pressure.

Total lumen to coronary flow determined by labelled cell counting showed similar results at coronary pressures below left ventricular systolic pressure (Fig. 8). The amount of flow was 10.2% in one animal at LV systolic pressure 80 mm Hg above coronary pressure. Total LV luminal contribution to the coronaries averaged 3.3% at LV systolic pressure 60 mm Hg above coronary pressure.

Figure 9 shows the mean calculated slopes for all experiments according to the input-output volume studies (%ΔV vol) and the labelled cell scintillation counting studies (%ΔV rad). At coronary pressures above LV systolic pressure, tagged blood appeared in the coronary drainage, i.e., blood from the left ventricular lumen entered the coronary circulation, although net flow of blood, according to the volume measurements, was from the coronary circulation to the left ventricular lumen. At most coronary pressures below LV systolic pressures,

left ventricular lumen to coronary flow determined by isotope counting was greater than that determined by volume measurement. This difference ranged from 2% greater at equal coronary and systolic pressures to 0% when coronary pressure was 70 mm Hg below systolic pressure.

The left ventricular end-diastolic pressure during these experiments ranged from 0 to 25, with an average of 7.1 mm Hg. No relationship was found between LVEDP and volume changes or pressure gradients.

The decontamination procedure described above effectively removed residual labelled blood from the coronary circulation. Calculations revealed that residual contamination averaged 0.3% of coronary flow, with a range of 0 to 1%, and a standard deviation of 0.12% of coronary flow. As previously stated, these values were subtracted from the results obtained during the experimental runs.

DISCUSSION

This experimental preparation was designed to overcome some of the difficulties encountered in the first approach to the study of coronary-luminal flow. As in Experiment I, this study was performed in the intact, working left ventricle; and the left coronary arterial system and the right side of the heart were completely

isolated to permit a quantitative measurement of coronary flow and drainage, while the coronary blood reservoir permitted experimental control of coronary pressures. Radioactively labelled erythrocytes demonstrated the passage of cellular elements, rather than just plasma or dye, through the myocardial sinusoidal channels and avoided the problem of diffusion of permeable substances through endocardial membranes.

To isolate the coronary circulation, it was necessary to remove all extracardiac sources of collateral blood supply to the heart. In this experiment, bronchial vessels were removed in addition to those removed in Experiment I, avoiding the necessity for control animals. Retrocardiac pericardial anastomoses, such as those at the entrance of the pulmonary veins to the left atrium, were not ligated. It is not fully known, however, how much flow occurs in these anastomoses, but it is generally thought that in non-diseased states these vessels play a very small role in the nourishment of the myocardium.

The calibrated coronary blood reservoir presented to the coronaries a constant pressure head during the entire cardiac cycle, and thus did not duplicate the physiologic pattern of flow in which aortic systolic and diastolic pressures are transmitted to the coronaries.

The artificial variation of coronary pressures above and below systolic pressure is also a deviation from the normal working conditions of the heart. As previously discussed, although coronary pressures above systolic are not encountered in physiologic conditions, extensive narrowing of the coronary arteries can produce significant lowering of arterial coronary pressure distal to the narrowing. Despite the experimental deviation from the normal physiologic condition, the results of this experiment indicate the capacity of the sinusoids to carry blood to the myocardium, and point to their possible role as collateral sources of blood supply in coronary artery disease.

This investigation demonstrated the passage of erythrocytes through channels (i.e., sinusoids) connecting the left coronary system and the left ventricular lumen. The net amount and direction of flow through these channels was proportional to the magnitude and direction of the coronary-luminal pressure gradient, as in Experiment I. In contrast to the net flow, scintillation counting revealed that flow from lumen to coronary occurred when coronary pressure exceeded ventricular systolic pressure. Further, at coronary pressures below ventricular systolic pressure, total flow from the LV lumen to coronary system, as determined by scintillation counting, exceeded net flow

in this direction. The difference between net flow and total flow represented blood flow opposite to the direction of the coronary-ventricular systolic pressure gradient; that is, from the coronaries to the left ventricular lumen.

The conclusions drawn from these results are that red blood cells flow through sinusoidal channels in both directions at all but extreme coronary-luminal pressure gradients, and that blood from the left ventricular lumen is continually entering the myocardium through these sinusoids.

Previously discussed investigations of the coronary-luminal channels both support and dispute the conclusions of this experiment. Wearn's anatomic studies (71) demonstrated "arterioluminal" and "arteriosinusoidal" connections between the coronary arteries and the left ventricular lumen. Later physiologic studies have brought these precise structures into question, and the exact structure of the sinusoidal channels is not yet fully known. The studies of Prinzmetal (54) demonstrated luminal channels up to 200 microns in diameter, while MacLean (42) was unable to find evidence of arterioluminal shunts greater than 20 microns in diameter. These sizes are capable of carrying red blood cells.

Katz and his associates (5) showed the transfer of

particles into the myocardium directly from the ventricles at coronary pressures both above and below systolic pressures. However, this study was not designed to demonstrate a quantitative relationship between coronary-ventricular pressure gradients and the amount of blood passing from the heart cavities to the myocardium. In contrast, Roberts (57) concluded that luminal vessels conducted dye from the ventricular cavities to the coronary vessels only when pressure in the ventricle exceeded pressure in the coronary arteries.

Watanabe (70) estimated the amount of left ventricular drainage to be several per cent of coronary flow. Ravin et. al., (55) calculated a coronary to left ventricular lumen shunt of less than 1%. The studies of Moir (45) showed that myocardial uptake of radioactively labelled saline from the left ventricular lumen amounted to about 7% of coronary flow during normal coronary and ventricular pressures. This flow was not increased by low coronary pressure alone or in combination with high left ventricular pressure, but did increase after total coronary occlusion.

Although anatomic studies have demonstrated the presence of thebesian vessels in the left atrium, Hammond and Austen (24) were unable to demonstrate left atrial drainage of coronary blood. It is not known whether the

left atrium contributed to sinusoidal flow in the present experiments, but it has been assumed that all sinusoidal flow occurred between coronary vessels and the left ventricular lumen.

How can the "to and fro" passage of blood between the left ventricular lumen and the coronary vessels, in apparent opposition to coronary-luminal pressure gradients, be explained?

When coronary pressure is below ventricular systolic pressure, sinusoidal blood can move in one or the other direction between lumen and coronaries at different phases of the cardiac cycle. Coronary pressure in this experiment was constant throughout the cardiac cycle, while contraction and relaxation of the ventricle produced a normal variation in ventricular lumen pressure during systole and diastole. During the height of systole, ventricular systolic pressure exceeded coronary pressure, and blood flowed from lumen to coronaries. During diastole, however, coronary pressure exceeded ventricular pressure, and blood flowed from the coronaries to the lumen of the left ventricle. The net flow of blood in the sinusoids was thus a balance of these two directional flows. As would be expected, though, total lumen to coronary flow, represented by the cross-over of labelled blood into the

coronary system, exceeded the net flow determined by the balance of luminal flow into and out of the myocardium.

The contraction of the ventricular myocardium acts primarily to pump blood from the lumen through the aorta and pulmonary vessels. It may also exert a milking effect on the intramural vessels during systole, forcing blood out of the vessels into superficial coronary veins and the heart cavities. Possibly, the reverse may occur at the onset of isometric relaxation of the ventricle, i.e., that blood may be drawn through the intramural coronary vessels from not only the superficial coronary vessels but also the cavity of the ventricle through the sinusoids. The inflow from the superficial coronary arteries would not necessarily prevent entrance of blood from the heart cavity, except when coronary pressure greatly exceeds ventricular pressure.

It is generally believed that the sinusoids make connections with each other, the capillary bed, the arterial system and the left ventricular chamber. It is likely then, that some luminal channels enter the coronary system distal to vasoactive arterioles, at points of low intravascular pressure, since the pressure drop from small artery to vein can be 100 mm/Hg or more. Thus, the pressure gradient across the sinusoids may in some cases be a luminal-

capillary gradient rather than a luminal-coronary artery gradient, and may continually permit sinusoidal blood transport from lumen to myocardium, down a pressure gradient, even though the coronary arterial pressure exceeds ventricular pressure. Further, this blood would pass through capillaries, thus would contribute to the oxygen needs of the myocardium.

CONCLUSIONS

These experiments show the capacity of the myocardial sinusoids to transport blood between the left ventricular lumen and the coronary vascular system.

They demonstrate a quantitative, linear relationship between sinusoidal flow and the coronary-luminal pressure gradient. This relationship has been demonstrated over a wide range of pressure gradients.

Net flow through the myocardial sinusoids is in the direction of and proportional to the direction and magnitude of the coronary-luminal pressure gradient. Sinusoidal flow amounts to 4 to 6 per cent of coronary flow at large pressure gradients.

Study of total flow of sinusoidal blood into the myocardium indicates that the myocardium is continually receiving a small amount of blood from the lumen, at normal coronary and ventricular pressures, and when coronary pressure is elevated above ventricular pressure. When coronary pressure is approximately equal to ventricular systolic pressure, sinusoidal flow from lumen to myocardium amounts to 2 per cent of coronary flow.

These conclusions raise further speculation. These experiments measured only the luminal blood that entered the coronary vasculature and was drained through the right

side of the heart. It is possible that a much larger amount of luminal blood may enter the myocardium to nourish the heart, but that most of it flows back into the left ventricle, as occurs in primitive vertebrate hearts. It is likely that the sinusoids provide a major source of nourishment to the inner myocardium and the papillary muscles, as suggested by Myers and Honig (49). Wearn (72) reported cases of complete occlusion of the coronary ostia in living functioning hearts, in which the luminal channels seemed to be essential to the survival of the heart. Angiography has demonstrated large sinusoids draining the right ventricle in cases of elevated right ventricular pressure from congenital abnormalities (40). Coronary cineangiography repeatedly demonstrates complete or nearly complete occlusion of the coronary vessels in patients with coronary artery disease, whose hearts continue to function, although often poorly. It is possible, in these instances, that the coronary-luminal channels serve as one important source of collateral circulation. It must be considered that the myocardial sinusoids play a role in the nourishment of the normal heart, and may provide one important source of additional blood supply should blood from the myocardium's major vessels, the coronary arteries, become diminished.

TABLE I

Computed slopes, intercepts, and 95% confidence intervals for the slope of each dog in the experimental group.

Exp. No.	Slope	Intercept	95% Confidence Intervals
1	+0.14	-5.2	±0.154
2	+0.098	-0.1	±0.018
3	+0.031	-5.9	±0.005
4	+0.240	+6.1	±0.069
5	+0.082	+1.4	±0.045
6	+0.066	-0.3	±0.089
7	+0.075	+3.5	±0.073
8	+0.064	+1.4	±0.055
9	+0.222	+30.0	±0.014
10	+0.116	+0.1	±0.062
11	+0.073	+2.8	±0.028
Mean	+0.077	+3.5	±0.007

TABLE II

Computed slopes, intercepts, and 95% confidence intervals for the slope of each dog in the control group.

Control No.	Slope	Intercept	95% Confidence Intervals
A	+0.059	-0.7	±0.025
B	-0.003	-2.7	±0.020
C	+0.014	-1.1	±0.018
D	+0.039	-0.3	±0.028
E	+0.008	-0.5	±0.031
F	-0.026	-1.5	±0.021
Mean	+0.010	-1.4	±0.008

TABLE III

Results determined according to input-output volume technique (%$\triangle$V vol). Computed slopes, intercepts and 95% slope confidence intervals for each dog.

Exp. No.	Slope	Intercept	95% Confidence Intervals
1	+0.094	+0.6	$\pm$0.021
2	+0.055	+0.6	$\pm$0.087
3	+0.061	+1.2	$\pm$0.043
4	+0.056	+1.4	$\pm$0.038
5	+0.068	+0.0	$\pm$0.048
6	+0.066	-1.0	$\pm$0.041
7	+0.051	-2.0	$\pm$0.037
8	+0.067	-0.7	$\pm$0.032
9	+0.044	-1.4	$\pm$0.033
10	+0.062	-0.5	$\pm$0.044
Mean	+0.058	-0.4	$\pm$0.009

TABLE IV

Results determined according to labelled red cell scintillation counting technique (% $\triangle$ V rad). Computed slopes, intercepts, and 95% slope confidence intervals for each dog.

Exp. No.	Slope	Intercept	95% Confidence Intervals
1	+0.063	+5.4	$\pm$0.028
2	+0.024	+2.6	$\pm$0.021
3	+0.051	+2.0	$\pm$0.033
4	+0.009	+1.7	$\pm$0.013
5	+0.034	+2.1	$\pm$0.026
6	+0.027	+0.9	$\pm$0.019
7	+0.008	+0.9	$\pm$0.011
8	+0.013	+1.3	$\pm$0.012
9	+0.027	+0.8	$\pm$0.022
10	+0.020	+2.1	$\pm$0.019
Mean	+0.025	+1.8	$\pm$0.008

1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

ILLUSTRATIONS

Fig. 1 Preparation in the data gathering configuration for Experiment I. The left ventricle is maintaining cardiac output and the left coronary artery is perfused from the graduated pressure reservoir.

Fig. 2 Per cent contribution of left ventricular luminal blood to the coronary circulation and per cent drainage of coronary blood into the left ventricular lumen in relation to coronary pressure above and below left ventricular systolic pressure. The calculated line for each experiment is shown.

Fig. 3 Per cent contribution to the coronary circulation by extracardiac collaterals and per cent drainage of coronary blood into the extracardiac collaterals in relation to coronary pressure above and below systolic pressure. The calculated line for each experiment is shown.

Fig. 4 Mean calculated contribution to and drainage from the coronary circulation in relation to coronary pressure above and below systemic pres-

sure in the control group or above and below LV systolic pressure in the experimental group.

Fig. 5 Flow through coronary arteries and myocardial sinusoids in cc/min/100 gms of heart muscle in relation to the coronary-LV systolic pressure gradient. In relation to sinusoidal transport, flow below the 0 cc/min line represents flow into sinusoids from the left ventricular lumen, while flow above the 0 cc/min line represents drainage through the sinusoids into the left ventricular lumen.

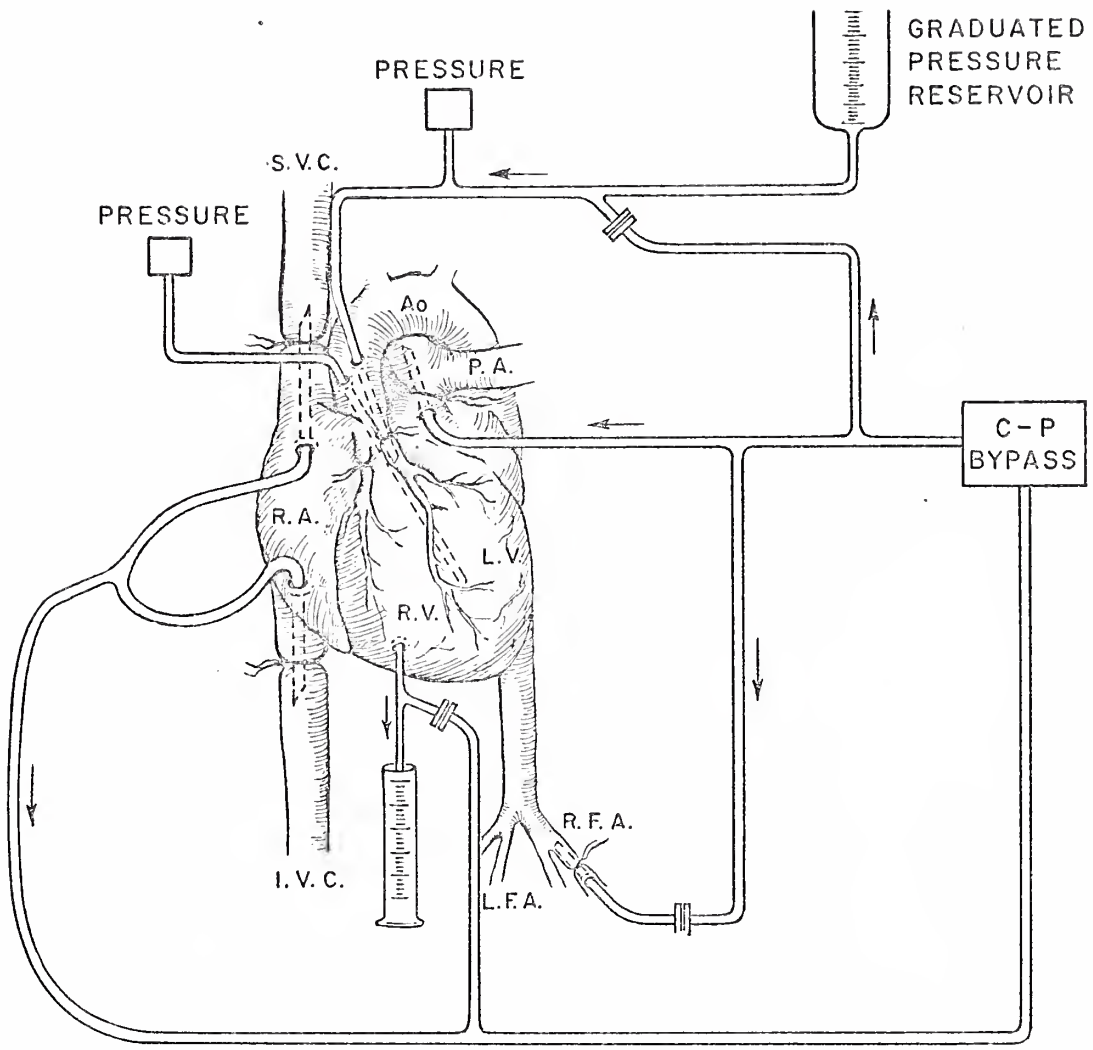
Fig. 6 Preparation in the data gathering configuration for Experiment II. The left ventricle is maintaining cardiac output and the left coronary artery is perfused from the graduated pressure reservoir. A support animal supplies unlabelled blood to the reservoir. The systemic circulation contains Cr^{51} labelled red blood cells.

Fig. 7 Per cent net contribution of left ventricular luminal blood to the coronary circulation and per cent net drainage of coronary blood into the left ventricular lumen in relation to coronary pressure above or below left ventricular

systolic pressure. Per cent values determined according to input-output volume technique. The calculated line for each experiment is shown.

Fig. 8 Per cent total contribution of left ventricular luminal blood to the coronary circulation in relation to coronary pressure above or below left ventricular systolic pressure. Per cent values determined according to labelled cell scintillation counting technique. The calculated line for each experiment is shown.

Fig. 9 Mean calculated per cent contributions to and drainage from the coronary circulation in relation to coronary pressure above or below left ventricular systolic pressure. Per cents determined by input-output volume technique (% Δ V vol) and labelled cell scintillation counting technique (% Δ V rad).


GRADUATED
PRESSURE
RESERVOIR
PRESSURE
S.V.C.
PRESSURE
Ao
P.A.
C-P
BYPASS
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R.V.
R.F.A.
I.V.C.
L.F.A.

Fig. 1

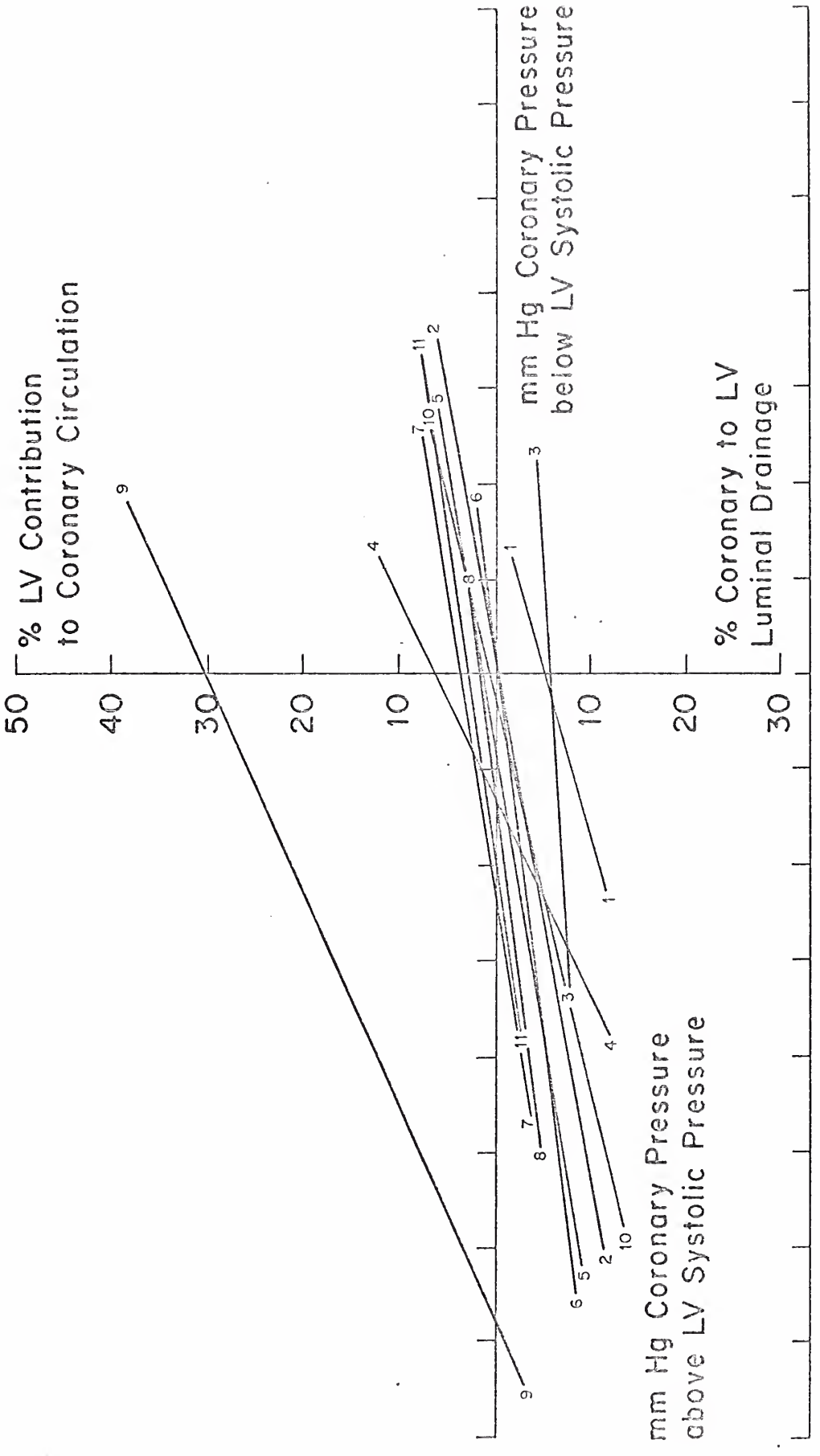
% LV Contribution
to Coronary Circulation
50
40
30
20
10
mm Hg Coronary Pressure
below LV Systolic Pressure
10
20
% Coronary to LV
Luminal Drainage
30
0
40
80
120
160
mm Hg Coronary Pressure
above LV Systolic Pressure
120
80
40

Fig. 2

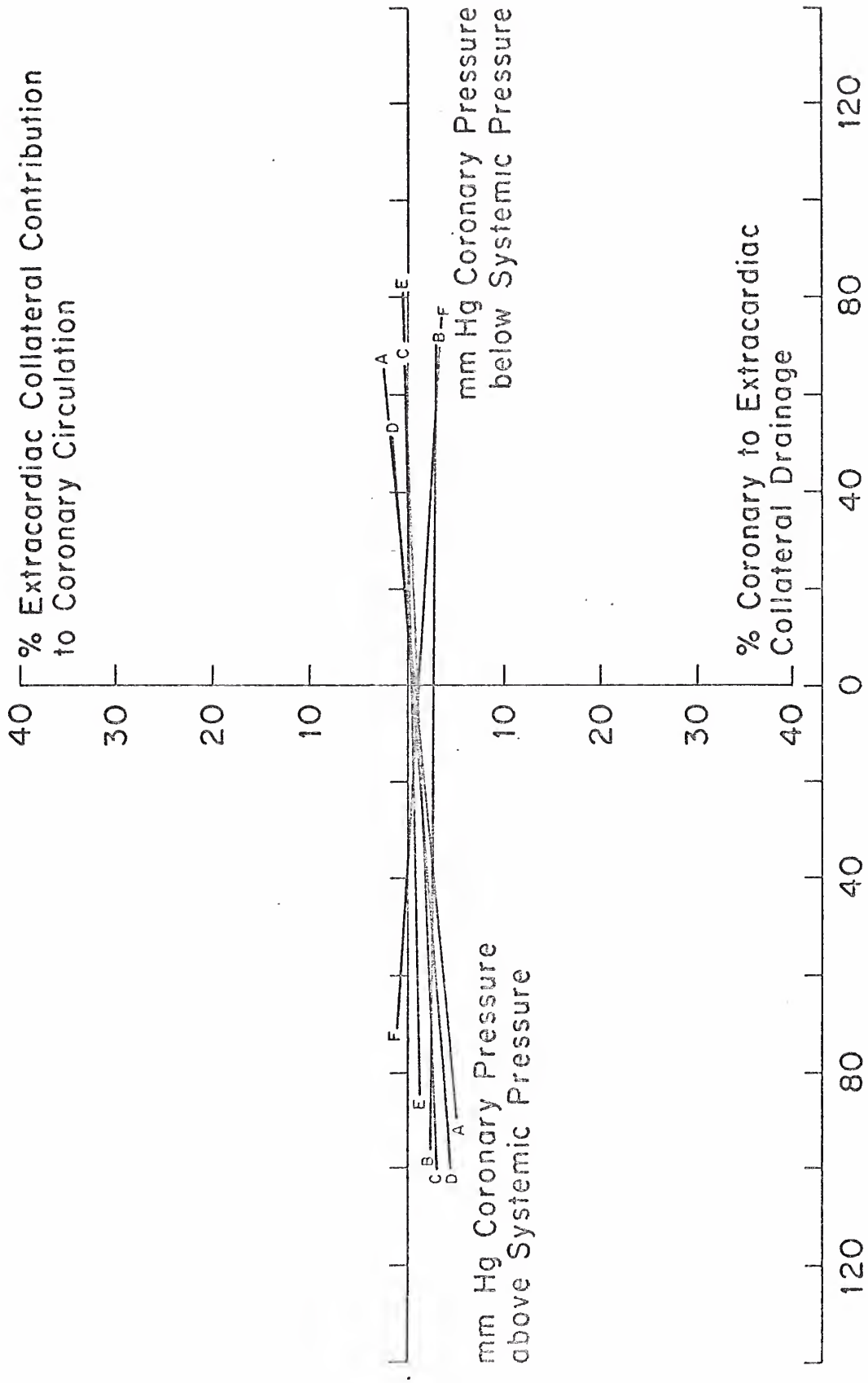
% Extracardiac Collateral Contribution to Coronary Circulation
40
30
20
10
mm Hg Coronary Pressure above Systemic Pressure
F
E
C
B
D
A
mm Hg Coronary Pressure below Systemic Pressure
10
20
30
40
A
D
C
E
B–F
% Coronary to Extracardiac Collateral Drainage
0
40
80
120
120
80
40

Fig 3

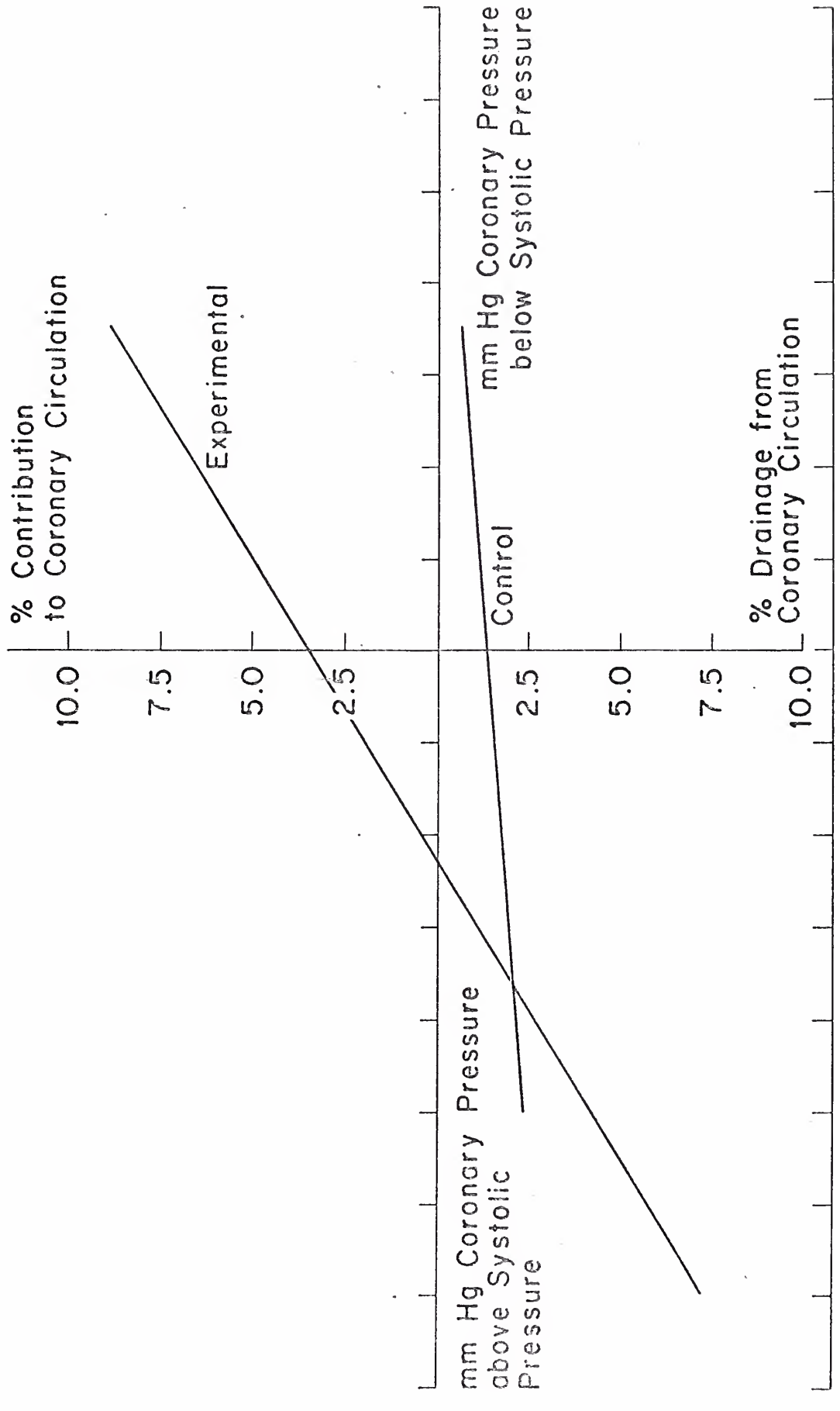
% Contribution to Coronary Circulation
Experimental
Control
mm Hg Coronary Pressure below Systolic Pressure
% Drainage from Coronary Circulation
mm Hg Coronary Pressure above Systolic Pressure
10.0
7.5
5.0
2.5
0
40
80
120
160

Fig. 4

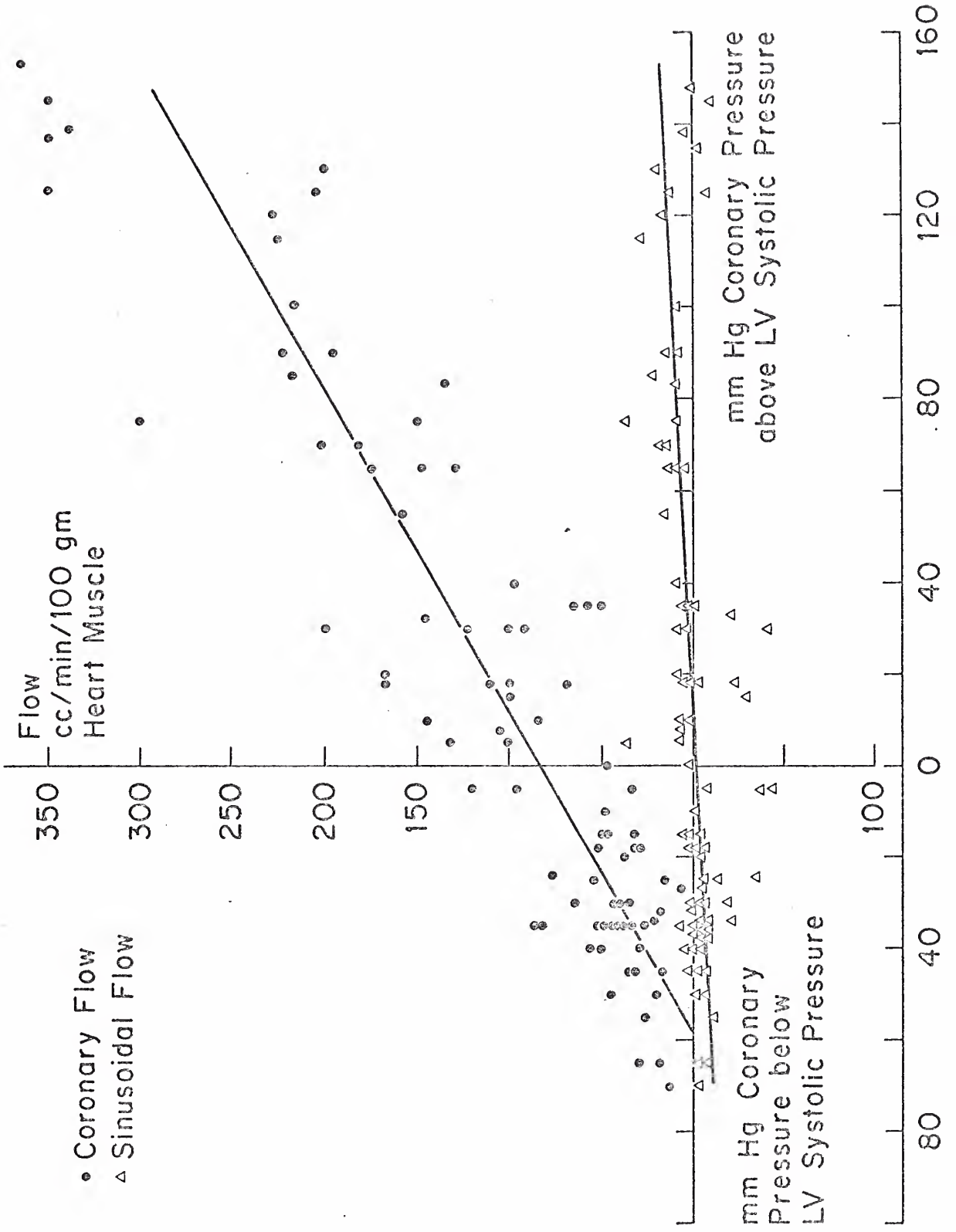
Flow
cc/min/100 gm
Heart Muscle
350
300
250
200
150
100
80
40
0
40
80
120
160
• Coronary Flow
△ Sinusoidal Flow
mm Hg Coronary
Pressure below
LV Systolic Pressure
mm Hg Coronary Pressure
above LV Systolic Pressure

Fig. 5

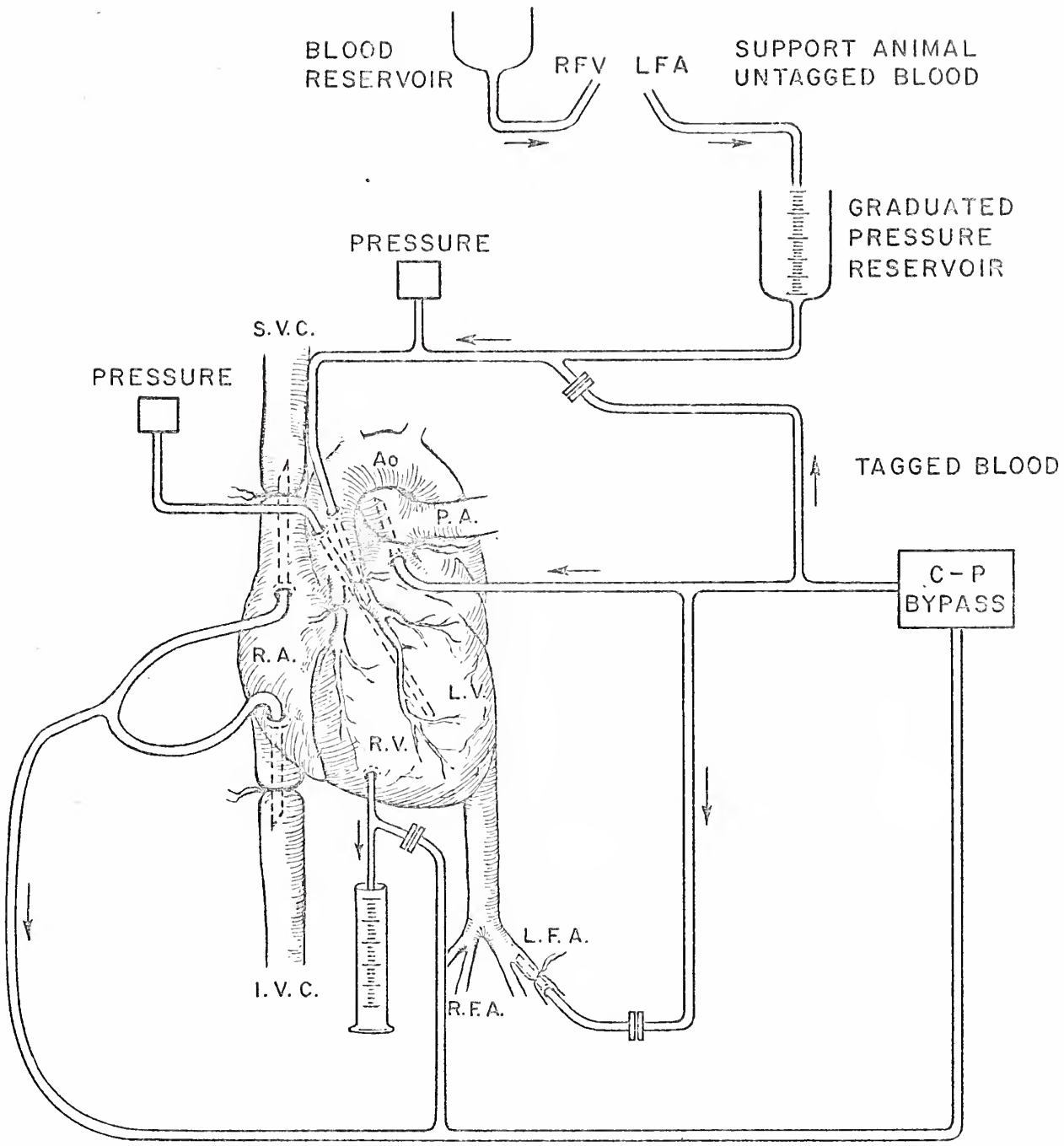
BLOOD
RESERVOIR
RFV
LFA
SUPPORT ANIMAL
UNTAGGED BLOOD
GRADUATED
PRESSURE
RESERVOIR
PRESSURE
S.V.C.
PRESSURE
Ao
P.A.
TAGGED BLOOD
C-P
BYPASS
R.A.
L.V.
R.V.
L.F.A.
I.V.C.
R.F.A.

Fig. 6

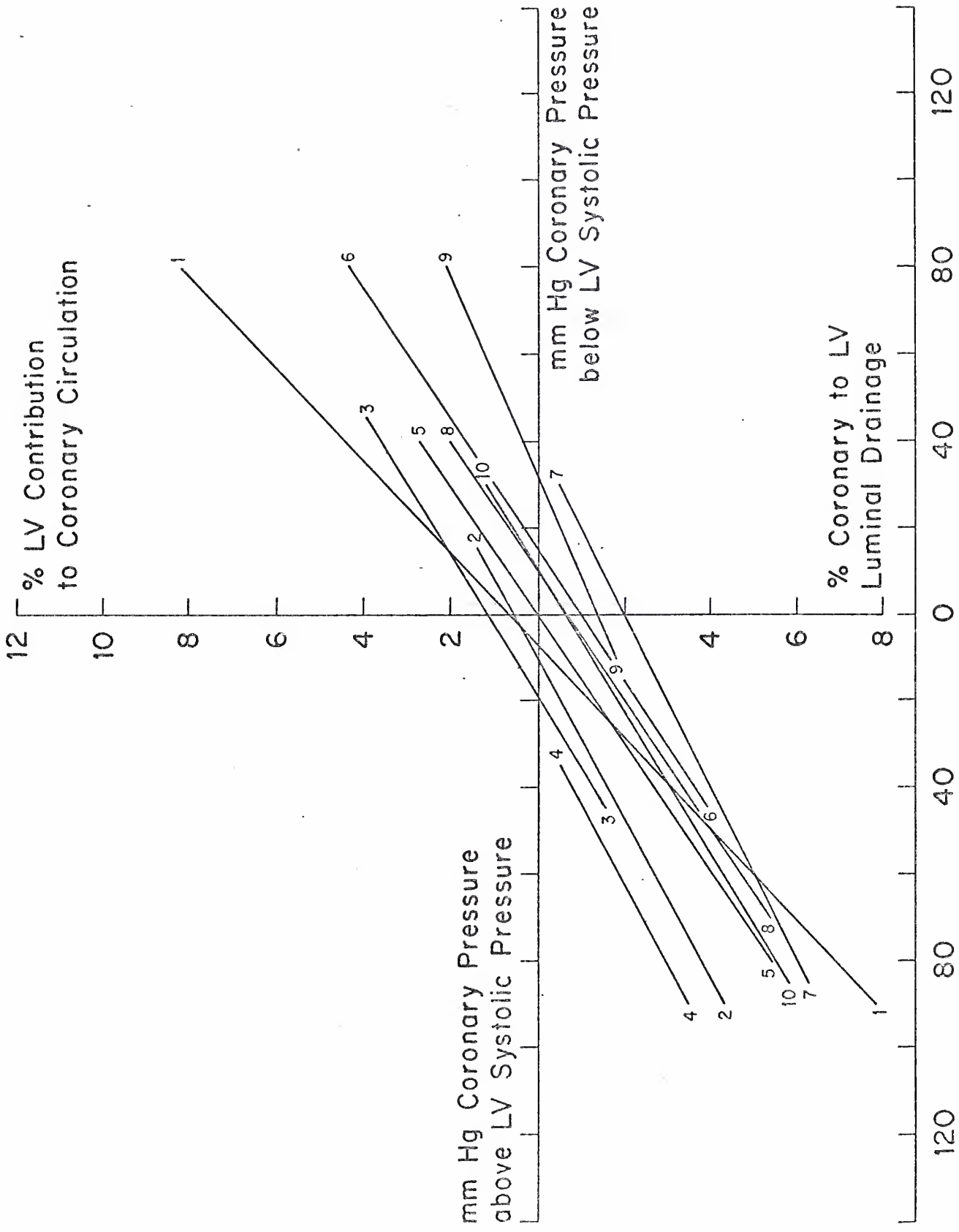
% LV Contribution
to Coronary Circulation
12
10
8
6
4
2
mm Hg Coronary Pressure
above LV Systolic Pressure
mm Hg Coronary Pressure
below LV Systolic Pressure
0
2
4
6
8
% Coronary to LV
Luminal Drainage
40
80
120
1
2
3
4
5
6
7
8
9
10

Fig. 7

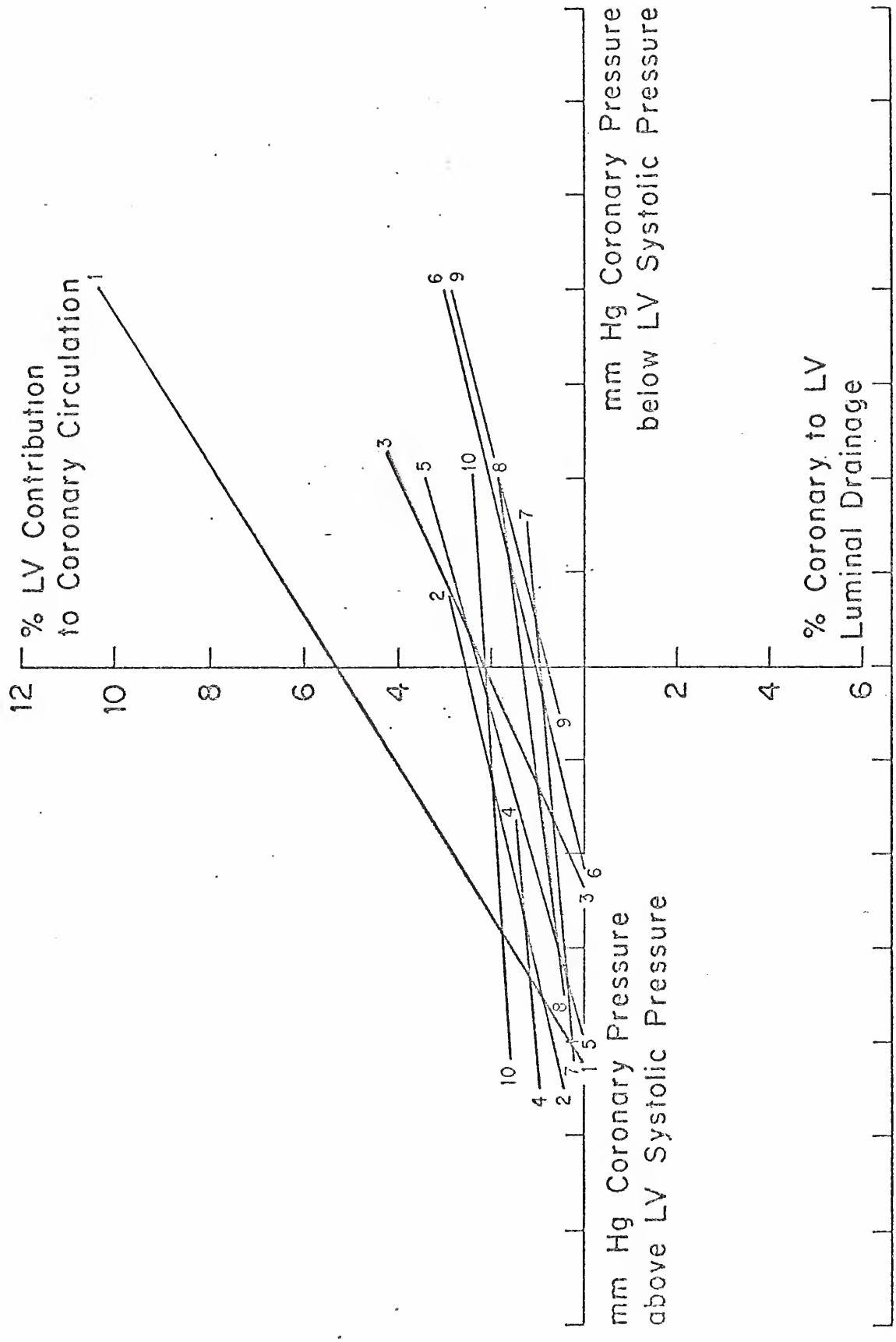
% LV Contribution
to Coronary Circulation
12
10
8
6
4
2
mm Hg Coronary Pressure
above LV Systolic Pressure
mm Hg Coronary Pressure
below LV Systolic Pressure
0
2
4
6
% Coronary to LV
Luminal Drainage
40
80
120

Fig. 8

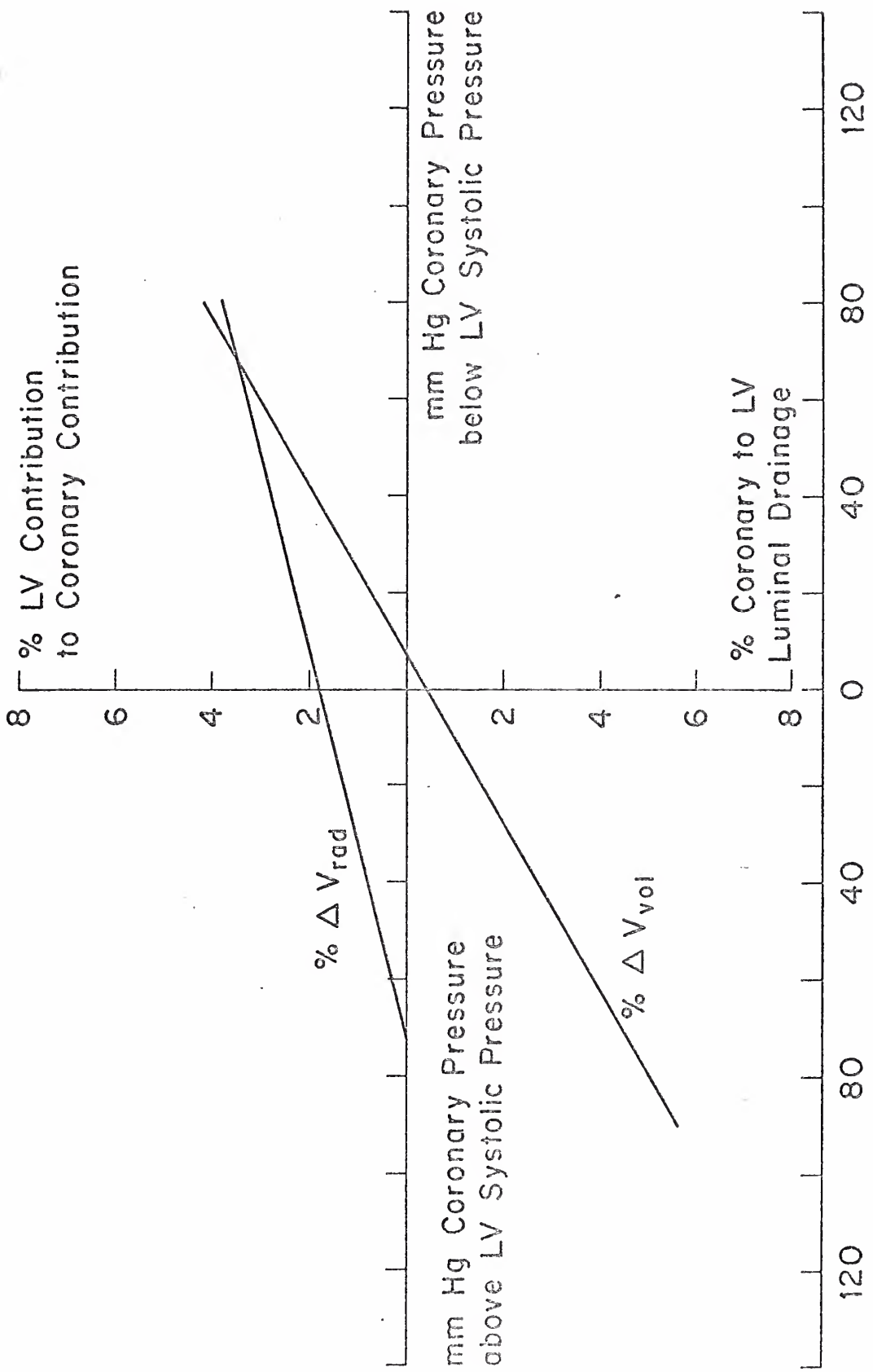
% LV Contribution
to Coronary Contribution
8
6
4
2
% Δ V_{rad}
mm Hg Coronary Pressure
above LV Systolic Pressure
120
80
40
0
mm Hg Coronary Pressure
below LV Systolic Pressure
2
4
6
8
% Δ V_{vol}
% Coronary to LV
Luminal Drainage
120
80
40
0

Fig. 9

ABSTRACT, EXPERIMENT I

The blood transport capabilities of myocardial sinusoids were studied in the intact, working left ventricle. The open chest dog was maintained on right heart bypass while the left ventricle maintained systemic circulation. The left coronary artery was perfused from a graduated, variable pressure reservoir. The right coronary artery was ligated. Venous drainage from the coronary sinus, anterior cardiac veins and thebesian veins was collected from a cannula placed in the right ventricle. Balance studies were then performed while varying coronary pressure from 140 mm Hg above to 80 mm Hg below left ventricular systolic pressure. The results showed that as coronary pressure increased over left ventricular systolic pressure an increasing percentage of coronary blood drained directly into the ventricular chamber. As coronary pressure fell below systolic pressure an increasing percentage of left ventricular luminal blood entered the myocardium and contributed to the coronary circulation.

ABSTRACT, EXPERIMENT II

The transfer of blood through coronary-luminal pathways (myocardial sinusoids) was studied in the intact, working left ventricle.

The open chest dog circulating Cr-51 labelled red blood cells was maintained on right heart bypass. The right coronary artery was ligated. The left coronary artery was perfused through a calibrated, variable pressure reservoir containing non-radioactive blood. Coronary pressure was varied from 90 mm/Hg above to 80 mm/Hg below left ventricular systolic pressure. Coronary drainage to the right heart was collected through a cannula placed in the right ventricle.

Red blood cell transfer from the left ventricular lumen to the myocardium occurred at all pressure gradients, including those in which coronary pressure exceeded left ventricular systolic pressure. Net volume and direction of flow through the myocardial sinusoids was determined by the magnitude and direction of the coronary-ventricular lumen pressure gradient. Sinusoidal flows averaged 4-6% at large pressure gradients.

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